Transformation of 5-Hydroxy- to (5-Chloropentanoyl)amino Derivatives under 'Direct Amide Cyclization' Conditions

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Abstract: The application of the 'direct amide cyclization' conditions to the linear delta-hydroxy diamide 11 is described (Scheme 3). Instead of the cyclization to the expected nine-membered cyclodepsipeptide, only the chloro acid 12 was obtained. Its formation could be explained by consecutive formation of the 1,3-oxazol-5(4H)-one 16 and the six-membered imino lactone 17 as intermediates (Scheme 4). The spontaneous isomerization of the latter gave 12 in a good yield.

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Transformation of 5-Hydroxy- into 5-Chloropentanoylamino Derivatives under 'Direct Amide Cyclization' Conditions

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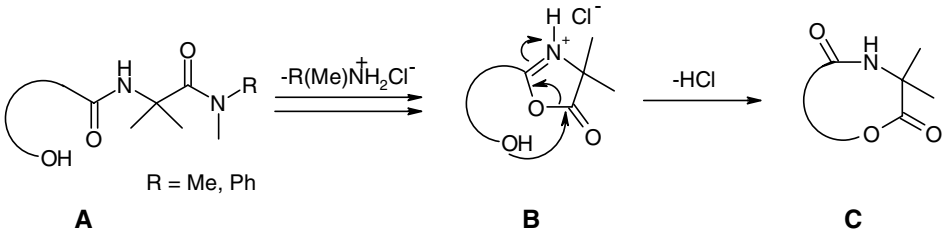
1. Introduction

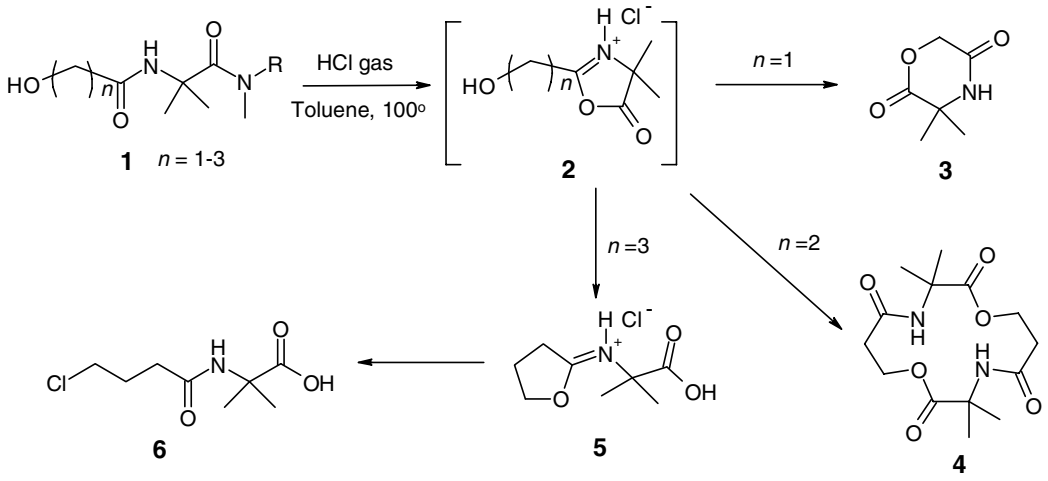
Cyclic depsipeptides are a class of biologically active secondary metabolites, which contain not only amide bonds as part of their ring structure, but also other bonds, usually lactone bonds. Their biological activity is diverse, being based mainly on their capability to transport selectively metal ions through cell membranes, and they are sought after as potential anticancer, antiviral, antibiotic and anti-inflammatory drugs [1].

One of the many methods known for their synthesis is the direct amide cyclization [2]: a suspension of an amide of type **A** in toluene is treated with dry HCl gas. Cyclization by elimination of the corresponding ammonium chloride leads to the intermediate 1,3-oxazol-5(4*H*)-one of type **B**. In the absence of other nucleophiles, **B** undergoes a ring enlargement *via* intramolecular nucleophilic attack of the hydroxy group at the carbonyl C-atom of the neighboring lactone group, to give the cyclodepsipeptide **C** (*Scheme 1).*



Scheme 1

This method has been used successfully for the synthesis of 6-, 9-, 12- and 15-membered [3] and larger ring systems [4]. For example, α-hydroxy acid derivatives of type **1** (*n* = 1) under the 'direct amide cyclization' conditions led to morpholinediones of type **3** [5] (*Scheme 2)*. Recently, we have shown that diamides of type **A**, which contain β-hydroxy acids, *i.e.* **1** (*n* = 2), under these reaction conditions did not give the expected 7-membered cyclodepsipeptides, and only their dimers, the 14-membered rings **4** were isolated in good yields [6][7] (*Scheme 2*). Treatment of γ-hydroxy acid derivatives (**1**, *n* = 3) with HCl gas in toluene yielded no cyclodepsipeptides at all. Instead, the only products isolated were the hydrochlorides of imino lactones **5,** which are unstable in solution and isomerize in polar solvents or on silicagel to give the chlorinated acids **6** [8] (*Scheme 2*).

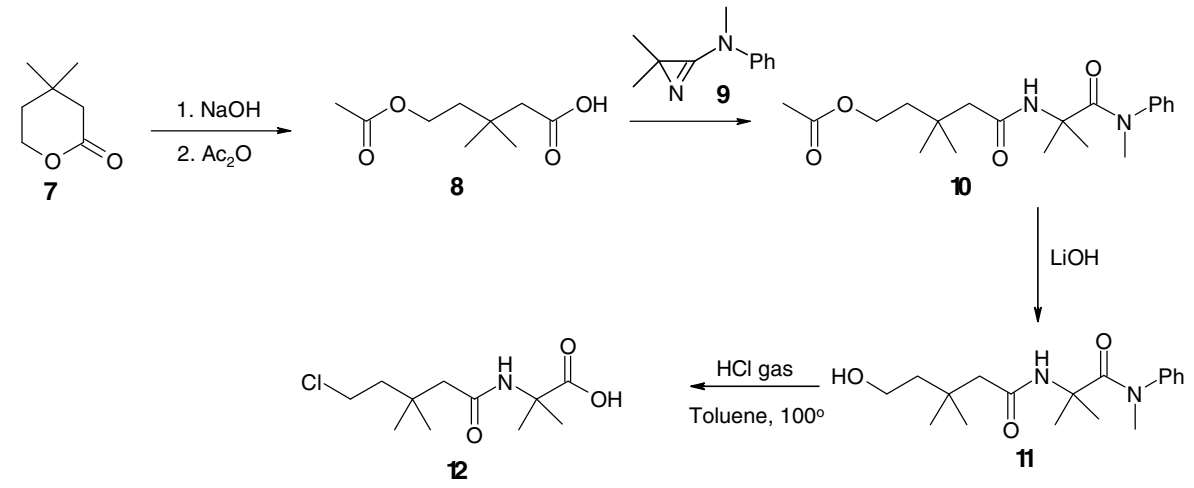


Scheme 2

In all cases so far, the formation of the intermediate oxazolone **2** was proven chemically or by IR spectroscopy. The results show that there is a relationship between the number of C-atoms between the OH and CONH groups and the type of product formed. Therefore, it was of interest to subject δ-hydroxy acid amides **1** (n = 4) to the conditions of the 'direct amide cyclization', which could yield either a 9- or 18-membered cyclodepsipeptide on the one hand, or a 6-membered imino lactone on the other. The result of a first example is shown below.

2. Results and Discussion

Since the previously used standard methods for syntheses of β- and γ-hydroxy acids [8] were not applicable to their δ-hydroxy analogues, we used the method of *Goto et al.* [9]: 3,3-dimethyl-γ-butyrolactone **7** was treated with NaOH and Ac_2O, which led to the O-protected 5-acetoxy-3,3-dimethylpentanoic acid (**8**) in moderate yield (*Scheme 3*).



Scheme 3

The reaction of the acid **8** with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**9**) [10] yielded the protected diamide **10.** After deprotection with LiOH, **11** was subjected to the 'direct amide cyclization' (DAC) conditions (HCl gas, toluene, 100°). Trituration of the crude product with CH_2Cl_2, a procedure that has allowed the isolation of the imino lactone hydrochlorides **5** without isomerization to the corresponding chlorinated acids [8], yielded in the present case the chloro acid **12** directly as the only product in good yield. Recrystallization from MeCN gave crystals which were suitable for an X-ray crystal structure determination (*Fig*. 1).

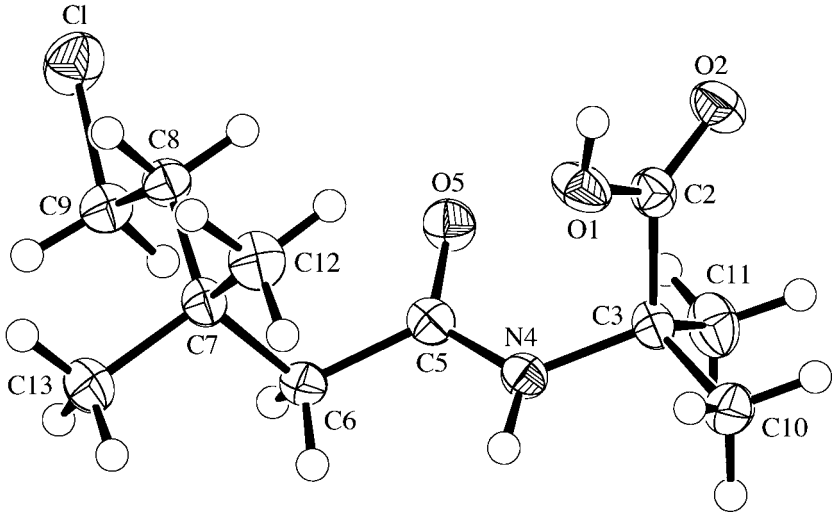


Fig. 1. ORTEP *Plot* [11] *of the molecular structure of* **12** *(arbitrary numbering of the atoms; 50% probability ellipsoids)*

Although the compound is achiral, it has crystallized in a polar space group and the absolute structure has been determined unambiguously. The OH group forms an intermolecular H-bond with the amide O-atom of a neighboring molecule, thereby linking the molecules into extended chains, which run parallel to the [0 1 0] direction and can be described by a graph set motif [12] of C(7). The amide group forms an intermolecular H-bond with the carboxylate carbonyl O-atom of a different neighboring molecule. This interaction links the molecules into extended chains, which run parallel to the [1 0 0] direction and can be descdibed by a graph set motif of C(5). The combination of both interactions generates a two-dimensional framework that lies parallel to the (0 0 1) plane (*Fig. 2*).

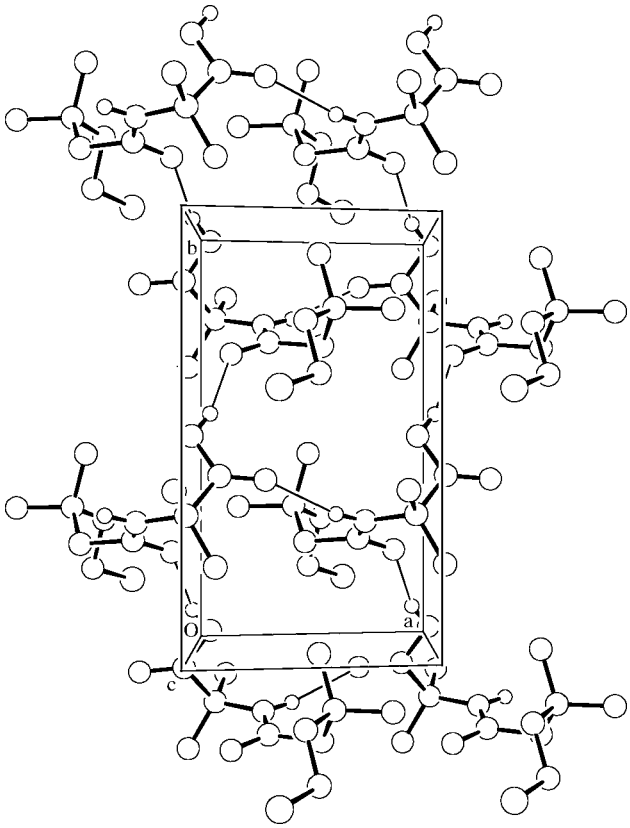
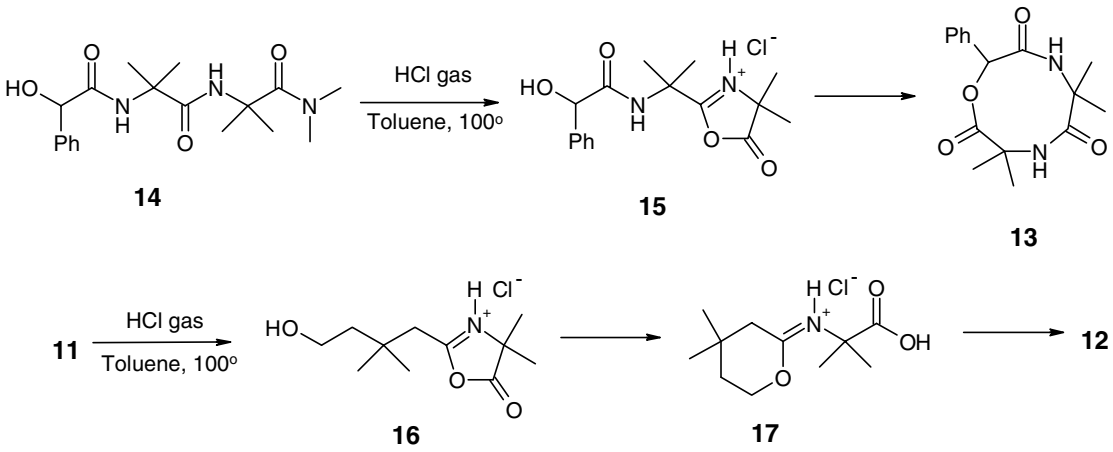


Fig. 2. *Molecular packing of* **12**, *showing the H-bonding interactions*

In our earlier studies, the ring size has a controlling influence over which of the possible products is formed from compounds of type **1** under the DAC conditions. With β-hydroxy acids (*n* = 2, *Scheme 2*) 14-membered rings **4** (cyclodimers) are preferred over 7-membered ones, while the formation of 5-membered imino lactones **5** is preferred over the corresponding 8-membered

cyclodepsipeptides in the case of γ-hydroxy acids (n = 3). Therefore, the expected product in the case where **1** contains a δ-hydroxy acid was either a 6-membered imino lactone analogous to **5,** or a 9-membered cyclodepsipeptide. As the 9-membered cyclodepsipeptide **13** has already been synthesized *via* DAC from the linear precursor **14** [3][13] (*Scheme 4*), the formation of **12** was a surprise.



Scheme 4

The formation of **12** proceeds most probably through the intermediate 1,3-oxazolone derivative **16** and the 6-membered imino lactone **17**, which apparently is unstable under these conditions and, by analogy with **5,** isomerizes spontaneously to give the chloro acid **12.**

3. Conclusions

The DAC conditions were applied to the linear precursor **11,** which contains a δ-hydroxy acid. Surprisingly, no cyclic depsipeptide was formed under these conditions. Thus, the dependence of the result of the DAC reaction on whether an α-, β-, γ-, or δ-hydroxy acid diamide is used has been confirmed. The general use of the 'direct amide cyclization' for the synthesis of cyclic depsipeptides is apparently limited to linear precursors which contain α-hydroxy acid amides. The use of β-hydroxy acid precursors is also possible for the formation of larger rings [4], but can lead to cyclodimers or side products as well.

Experimental Part

1. *General*. See [8].

2. *Starting materials*. 2,2,*N*-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**9**) was prepared according to standard procedures (*cf.* [8] and refs. cited therein). Butyrolactone **7** was prepared by a known method [14].

3. *5-Acetoxy-3,3-dimethylpentanoic acid* (**8**). To a soln. of **7** (20 mmol, 2560 mg) in MeOH (10 ml) was added 2N NaOH (11 ml) at 0°. The mixture was stirred at r.t. for 2 h, the solvent evaporated *i.v.* and the remaining H_2O was distilled azeotropically with benzene (3 x 10 ml). The white residue was dried overnight under *h.v.* and then Ac_2O (10 ml) was added. After 14 h at 80°, the mixture was cooled, the solvent evaporated and the oily residue extracted with AcOEt (5 x 30 ml). Drying ($MgSO_4$) and CC on SiO_2 with CH_2Cl_2/MeOH 20:1 yielded 1201 mg (32%) of **9.** Recovered starting material: 980 mg (37%). IR: 3288*s* (br), 2971*s*, 1738v*s*, 1711v*s*, 1471*w*, 1378*s*, 1356*m*, 1244*s*, 1094*s*, 1040*s*, 925*w*. ^{1}H-NMR: 0.97 (*s*, Me_2C); 1.59-1.71 (*m*, CH_2); 1.99 (*s*, MeCO); 2.21 (*s*, CH_2); 4.01 (br. *s*, CH_2O); 10.41 (br. *s*, COOH). ^{13}C-NMR: 20.7 (*q*, *Me*CO); 27.2 (*q*, *Me*$_2$C); 32.0 (*s*, Me_2C), 37.6, 43.9 (2*t*, 2 CH_2); 66.6 (*t*, CH_2O); 171.1 (*s*, C=O); 177.3 (*s*, COOH). ESI-MS: 211 (100, $[M + Na]^+$).

4. *4-[1-Methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethylcarbamoyl)-3,3-dimethylbutyl Acetate* (**10**). To a soln. of **8** (376 mg, 2 mmol) in dry THF (20 ml), **9** (365 mg, 2.1 mmol) was added. The mixture was stirred at r.t. overnight and the solvent evaporated *i.v.* CC with CH_2Cl_2/MeOH 40:1 yielded 622 mg (86%) of **10**. White powder. M.p. 98.1-99.4°. ^{1}H-NMR: 0.97, 1.41 (2*s*, 2 Me_2C); 1.62 (*t*, *J* = 7.1, CH_2); 1.99 (*s*, MeCO); 2.08 (*s*, CH_2); 3.19 (*s*, MeN); 3.1 (*t*, *J* = 7.1, CH_2O); 6.55 (*s*, NH); 7.20-7.39 (*m*, 5 arom. H). ^{13}C-NMR: 20.8 (*q*, *Me*CO); 26.3, 27.0 (2*q*, 2 *Me*$_2$C); 33.0 (*s*, Me_2C); 41.3 (*t*, CH_2); 42.3 (*q*, MeN); 48.2 (*t*, CH_2); 58.1 (*s*, Me_2C); 68.7 (*t*, CH_2O); 127.8, 128.0, 129.3 (3*d*, 5 arom. CH); 144.6 (*s*, arom. C); 169.8, 171.6, 173.2 (3*s*, 3 C=O). ESI-MS: 385 (100, $[M + Na]^+$]).

5. *5-Hydroxy-3,3-dimethyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-pentanamide* (**11**). A soln. of **9** (362 mg, 1 mmol) in THF/H_2O 2:1 (20 ml) was treated with 4 equiv. of LiOH at r.t. for 4 h. Evaporation of the solvent *i.v.*, extraction of the residue with CH_2Cl_2, drying ($MgSO_4$), evaporation *i.v.* and washing with Et_2O yielded the hydroxydiamide **11**, which was used without further purification. Yield: 298 mg (93%) of **11**. White solid. M.p. 128.4-126.0°. ^{1}H-NMR: 0.99, 1.46 (2*s,* 2 Me_2C); 1.60 (*t, J* = 7.1, CH_2); 2.00 (*s,* CH_2); 3.17 (*s,* MeN); 3.18 (*t, J* = 7.1, CH_2O); 6.51 (*s,* NH); 7.18-7.36 (*m,* 5 arom. H). ^{13}C-NMR: 26.4, 28.8 (2*q*, 2 *Me*$_2$C); 32.8 (*s,* Me_2C); 41.4 (*t*, CH_2); 42.4 (*q*, MeN); 48.2 (*t*, CH_2); 58.2 (*s,* Me_2C); 69.7 (*t*, CH_2O); 127.8, 128.0, 129.3 (3*d,* 5 arom. CH); 144.5 (*s,* arom. C); 171.7, 173.3 (2*s,* 2 C=O). ESI-MS: 343 (100, $[M + Na]^+$).

6. *2-(5-Chloro-3,3-dimethylpentanoylamino)-2-methylpropanoic Acid* (**12**). A suspension of **11** (80 mg, 0.25 mmol) in dry toluene (30 ml) was heated to 100° and HCl gas was bubbled through the suspension for 4-6 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca*. 20 min). The solvent was evaporated, the white residue was washed with CH_2Cl_2 (3 x 15 ml) and dried in *h.v*. Yield: 36 mg (59%) of **12**. M.p. 118.9-121.0°. IR: 3320v*s,* 2980*s,* 1722v*s,* 1620*s,* 1561*s,* 1466*s,* 1428*s*, 1389*m,* 1246*m*, 1232*m,* 1166*s,* 1092*m*, 1051*w,* 945*w.* ^{1}H-NMR ((D$_6$)DMSO): 0.97, 1.33 (2*s,* 2 Me_2C); 1.68-1.79 (*m,* CH_2); 1.97 (*s,* CH_2); 3.60-3.69 (*m*, CH_2Cl); 7.82 (br. *s,* NH); 11.81 (br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 24.8, 27.2 (*q*, *Me*$_2$C); 33.4, 42.5 (*t,* CH_2); 54.6 (*t*, CH_2Cl); 55.7 (*s,* Me_2C); 169.9, 175.4 (2*s,* 2 C=O). ESI-MS: 274 (25, $[M(^{37}Cl) + Na]^+$), 272 (100, $[M(^{35}Cl) + Na]^+$), 214 (10, $[M - Cl]^+$).

7. *X-Ray Crystal-Structure Determination of* **12** (*Table* and *Figs. 1,2*).[3]) All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [15] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table* and views of the molecules are shown in *Figs. 1* and *2*. Data reduction was performed with *HKL Denzo* and *Scalepack* [16]. The

[3]) CCDC- 286116 contains supplementary crystallographic data for this paper. These data can be obtained free of charge form the *Cambridge Crystallographic Data Centre, via* http://www.ccdc.cam.ac.uk/data_request/cif

intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [17] was applied. Equivalent reflections, other than *Friedel* pairs, were merged. The structure was solved by direct methods using *SIR92* [18], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The hydroxy and amide H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Refinement of the absolute structure parameter [19][20] yielded a value of 0.01(6), which confirms that the refined model represents the true absolute structure. Neutral atom scattering factors for non-H atoms were taken form [21] and the scattering factors for H-atoms were taken from [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f'' were those of [24]. The values of the mass attenuation coefficients are those of [25]. All calculations were performed using for the *SHELXL97* program [26].

Acknowledgements

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Table. *Crystallographic Data of* **12**

	12
Crystallized from	CH_3CN
Empirical formula	$C_{11}H_{20}ClNO_3$
Formula weight [g mol^{-1}]	249.74
Crystal color, habit	colorless, plate
Crystal dimensions [mm]	$0.02 \times 0.20 \times 0.25$
Temp. [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1$
Z	2
Reflections for cell determination	45269
2θ range for cell determination [°]	4–55
Unit cell parameters a [Å]	6.1314(3)
b [Å]	10.4871(5)
c [Å]	10.4750(5)
β [°]	104.760(2)
V [Å^3]	651.32(5)
D_x [g cm^{-3}]	1.273
μ(MoK_α) [mm^{-1}]	0.286
Scan type	ϕ and ω
2θ(max) [°]	55
Transmission factors (min; max)	0.864; 0.996
Total reflections measured	13304
Symmetry independent reflections	2950
Reflections with $I > 2\sigma(I)$	2548
Reflections used in refinement	2950
Parameters refined; restraints	159; 1
R [on F; $I > 2\sigma(I)$ reflections]	0.0372
wR [on F^2; all indept. reflections]	0.0814
Weighting parameters [a; b][a])	0.0314; 0.1588
Goodness of fit	1.044
Secondary extinction coefficient	0.035(5)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.19; -0.16

a) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$

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